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Decreased levels of serum oxytocin in pediatric patients with Attention Deficit/Hyperactivity Disorder

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ABSTRACT

Attention Deficit/Hyperactivity Disorder (ADHD) and autism spectrum disorder (ASD) are highly comorbid, and both disorders share executive function deficits. Accumulating evidence suggests that ASD patients have significantly lower peripheral oxytocin (OXT) levels compared with their normal counterparts, and that the repetitive behavior seen in ASD is related to abnormalities in the OXT system. In this study, we investigated whether serum levels of OXT are altered in pediatric patients with ADHD.

We measured serum OXT levels: drug naive ADHD ($n=23$), medicated ADHD ($n=13$), and age- and sex- matched, neurotypical controls ($n=22$). Patients were evaluated using the ADHD-RS. Serum levels of OXT in total subjects with ADHD were significantly decreased compared with those of neurotypical controls, and serum levels of OXT in drug naive ADHD patients were significantly lower than those in medicated ADHD patients. Interestingly, there was a significant negative correlation between serum OXT levels and ADHD-RS total scores, as well as ADHD-RS inattentive scores in all ADHD patients. In conclusion, this study suggests that decreased levels of OXT may play a role in the pathophysiology of patients with ADHD and its inherent inattentiveness.

1. Introduction

Attention Deficit/Hyperactivity Disorder (ADHD) is a common chronic psychiatric disorder, characterized by a pattern of developmentally inappropriate inattention, motor restlessness and impulsivity, which affects between 3 and 7% of school age children, according to DSM-IV criteria (American Psychiatric Association, 1994; Polanczyk et al., 2007). Prospective follow-up studies found that approximately 50% of children with ADHD show symptoms that continue into adulthood, and when left untreated, are associated with substance abuse, depression, unemployment and criminal offenses (Biederman et al., 2006; Molina et al., 2009). However, the precise neurobiological mechanisms underlying the pathophysiology of ADHD are currently unknown. One way to combat this disorder would be to discover novel biomarkers. Biomarkers would aid both diagnosis and the development of effective psychiatric treatment (Scassellati et al., 2012; Thome et al., 2012).

Autism spectrum disorder (ASD) is defined by impairment in communication and social interaction, as well as by restricted and repetitive behavior, according to DSM-IV criteria (American Psychiatric Association, 1994). Accumulating evidence suggests that ASD patients have significantly lower peripheral oxytocin (OXT) levels relative to healthy counterparts, and that the repetitive behavior in ASD is related to abnormalities in the OXT system, abnormalities which can be partially ameliorated by synthetic oxytocin infusion (Modahl et al., 1998; Hollander et al., 2003, 2007).

ADHD and ASD are highly comorbid and both disorders share executive function deficits (Willcutt et al., 2005, Corbett et al., 2009; Rommelse et al., 2011), including poor cognitive flexibility (Hill, 2004; Willcutt et al., 2005; Sanders et al., 2008), which has been linked to repetitive behavior in ASD (Yerys et al., 2009). The clinical importance of this behavioral and cognitive overlap has been highlighted by changes to the DSM-5, which now allows co-diagnosis of ADHD and ASD (American Psychiatric Association, 2013).

Abbreviations: ADHD, Attention Deficit/Hyperactivity Disorder; ASD, autism spectrum disorder; OXT, oxytocin

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It is reported that OXT gene knockout mice (mice lacking the gene for OXT) showed deficits in other behaviors, such as, decreased social investigation and increased aggression (Insel, O'Brien, and Leckman., 1999). It is also found that OXT gene knockout mice failed to develop social memory (Ferguson et al., 2000). These behaviors and disorders are similar to the symptoms of ADHD. Furthermore, it is suggested that ASD shares familial transmission with ADHD, and that ADHD and ASD share a partially overlapping diathesis (Musser et al., 2014). Based on these evidences, we hypothesized that serum levels of OXT in patients with ADHD are lowered than normal controls.

The objective of this study was to examine whether serum levels of OXT in pediatric patients with ADHD, differ from those of sex- and age-matched, neurotypical controls. In addition, we investigated the relationship between serum OXT levels and the clinical symptoms in ADHD patients.

2. Methods

2.1. Ethics statement

The ethics committee of Chiba University Graduate School of Medicine approved the study protocol (IRB number 137), which was performed in accordance with the Declaration of Helsinki II. All subjects and their parents provided written informed consent for study participation, after receiving a full explanation of the study, as well as any potential risks and benefits.

2.2. Study design and subjects

Thirty six pediatric patients with ADHD were recruited from the outpatients of Chiba University Hospital. Twenty-two, age- and sex- matched healthy, typically developing controls were recruited via advertisements, from Chiba city residents. All patients were diagnosed by child psychiatrist according to the DSM-IV criteria for ADHD (American Psychiatric Association, 1994), and were classified into three subtypes; inattentive subtype ($n=19$), combined (inattentive and hyperactive/impulsive) subtype ($n=16$) and hyperactive/impulsive subtype ($n=1$). None of the patients fulfilled any of ASD, and mood disorders (depressive disorders and bipolar disorders) according to DSM-IV criteria (American Psychiatric Association, 1994), while patients with other psychiatric comorbidities (learning disorders, tic disorders, oppositional defiant disorders) were included. Neurotypical controls ($n=22$) underwent a comprehensive medical history assessment to eliminate those with neurological and other medical disorders. The Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) was also conducted to exclude current and past, personal and familial histories of mental illnesses (Sheehan et al., 2010). None of the typically developing controls fulfilled any of these exclusion criteria.

Table 1
Demographics and clinical characteristics of ADHD subjects and neurotypical controls.

	ADHD total ($n=36$)	ADHD drug naïve ($n=23$)	ADHD medicated ($n=13$)	Neurotypical controls ($n=22$)	ADHD vs controls		ADHD drug naïve vs ADHD medicated vs controls	
					t	p	F	**p**
Age (years)	9.86 ± 2.332	10.30 ± 2.476	9.08 ± 1.891	10.91 ± 2.635	1.668	0.106[a]	2.338	0.106[b]
Age range (years)	6–15	6–15	6–14	7–15	–	–	–	–
Gender (male/female)	26/10	15/8	11/2	11/11	–	0.088[c]	–	0.118[c]
Race (% Japanese)	100	100	100	100	–	–	–	–
ADHD subtypes (combined/ inattentive/hyperactive–impulsive)	19/16/1	11/11/1	8/5/0	–	–	–	–	–
ADHD-RS Total Score	25.31 ± 11.459	26.65 ± 10.641	22.92 ± 12.874	–	–	–	–	–
ADHD-RS Hyper/Impulsive Score	10.47 ± 7.069	10.87 ± 6.864	9.77 ± 7.650	–	–	–	–	–
ADHD-RS Inattentive Score	14.83 ± 5.868	15.78 ± 5.681	13.15 ± 6.039	–	–	–	–	–
WISC-III/IV Full IQ Score	88.6 ± 15.272	88.70 ± 15.372	88.42 ± 15.756	–	–	–	–	–
Co-morbidity (number)	4	3	1	–	–	–	–	–
Learning disorder	1	1	0	–	–	–	–	–
Tic disorder	1	1	0	–	–	–	–	–
Oppositional defiant disorder	1	1	0	–	–	–	–	–
Learning disorder and oppositional defiant disorder	1	0	1	–	–	–	–	–
Pharmacotherapy (number)	13	–	13	–	–	–	–	–
Methylphenidate	6	–	6	–	–	–	–	–
Atomoxetine	3	–	3	–	–	–	–	–
Aripiprazole	2	–	2	–	–	–	–	–
Methylphenidate and Atomoxetine	2	–	2	–	–	–	–	–
Drug naïve (number)	23	23	0	22	–	–	–	–
Serum levels of oxytocin (pg/ml)	60.687 ± 37.143	49.295 ± 21.541	80.843 ± 49.842	99.876 ± 28.566	4.237	< 0.001*** [a]	14.068	< 0.001*** [d], (< 0.001*** [a,e], 0.048* [a,f], 0.072 [a,g])

Reported values are means ± S.D. (standard deviation), percentages, ranges.
Abbreviations: ADHD: Attention Deficit/Hyperactivity Disorder; ADHD-RS: Attention Deficits/Hyperactivity Disorder-Rating Scale IV Japanese version; WISC-III/IV: the Wechsler Intelligence Scale for Children-III/IV

* Statistically significant at $p < 0.05$.
*** Statistically significant at $p < 0.001$.
[a] Student's *t*-test and Mann–Whitney *U* test and Bonferroni correction post hoc were employed for continuous variables between the two groups.
[b] One-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test was used for comparisons among the ADHD medicated group, ADHD drug naïve group and healthy normal controls.
[c] χ^2 test.
[d] Kruskall–Wallis test,
[e] ADHD drug naïve vs neurotypical controls,
[f] ADHD drug naïve vs ADHD medicated,
[g] Neurotypical controls vs ADHD medicated.

2.3. Measurement of clinical symptoms

All patients were assessed using the ADHD-Rating Scale IV Japanese parents' version (ADHD-RS) (DuPaul et al., 2008). The ADHD-RS is a reliable and easy-to-administer instrument both for diagnosing ADHD in children and adolescents, and for assessing treatment response. Containing 18 items, the scale is linked directly to DSM-IV diagnostic criteria for ADHD (Tani et al., 2010). The Wechsler Intelligence Scale for Children – Third Edition (WISC-III) or Fourth Edition (WISC-IV), Japanese version was used to assess the Full Intelligent Quotient (FIQ) of patients with ADHD (David, 1998, 2010).

2.4. Measurement of OXT levels from serum

Serum samples from patients and typically developing control subjects were collected between 10:00 and 15:00 h, and stored at −80 °C until assayed. Serum OXT levels were measured using the OXT ELISA kit (Catalog no. ADI-900-153, ENZO Life Sciences, Farmingdale, NY, USA). In order to eliminate the effect of potentially interacting molecules, we performed a solid-phase extraction of serum samples. Briefly, an equal volume (250 μL) of 0.1% trifluoroacetic acid in water (TFA-H_2O) was added to serum samples (250 μL) and centrifuged at 17,000 × *g* for 15 min, at 4 °C. The supernatant was collected. C18 Sep-Pak columns (200 mg, Waters Corporation Milford, Massachusetts USA) were equilibrated with 1 mL of acetonitrile, followed by four applications with 3 mL of 0.1% TFA-H_2O. The supernatant was applied to the C18 Sep-Pak column, and washed four times with 3 mL of 0.1% TFA-H_2O, and the flow-through fraction was discarded. Next, the sample was eluted slowly by applying 3 mL of a solution comprising 60% acetonitrile and 40% 0.1% TFA-H_2O, and the eluent collected in a plastic tube. The solvent was evaporated using a centrifugal concentrator under vacuum at 4 °C, and the remaining sample was stored at −20 °C, before assay. The samples were reconstituted in assay buffer provided with the ELISA kit, and the assay was performed according to the manufacturer's protocol. Absorbance at 405 nm was then measured using an Emax automated microplate reader (Molecular Devices, Tokyo). All assays were performed in duplicate.

2.5. Statistical analysis

Statistical analyses were performed using the software package SPSS Version 21.0, for Macintosh (IBM Armonk, NY, USA). Chi-squared test was used for categorical variables. Student's *t*-test and Mann–Whitney *U* test were employed for continuous variables between the two groups. Levene's test was used to determine whether variables showed equal variance. One-way analysis of variance (ANOVA) followed by Tukey's multiple comparison was used for comparisons of age in the ADHD medicated and ADHD naïve groups, and neurotypical controls. Kruskall–Wallis test was used for comparisons of serum levels of OXT in the ADHD medicated and ADHD naïve groups, and neurotypical controls. Bonferroni correction was used for post hoc test. Pearson's and Spearman's correlation coefficients and forced entry multiple regression analysis were employed to detect correlations between serum OXT levels and clinical variables. Statistical significance was set at $P<0.05$ (two-tailed) with Power $(1-\beta)=0.80$. Wilcoxon–Mann–Whitney test with 36 total ADHD samples and 22 neurotypical control samples, 23 ADHD naïve samples, 13 ADHD medicated samples would have enabled us to detect the following effect sizes: total ADHD vs neurotypical controls; $d=0.79$ (medium-to-large), ADHD naïve vs ADHD medicated; $d=1.03$ (large), ADHD naïve vs neurotypical controls; $d=0.86$ (large), ADHD medicated vs neurotypical controls; $d=1.03$ (large).

3. Results

3.1. Sample characteristics

Demographic and clinical characteristics of ADHD subjects and typically developing controls are shown in Table 1. Age and gender status did not differ between total subjects with ADHD and neurotypical controls. Age and gender also did not differ among the neurotypical control group, the drug naïve ADHD and the drug medicated ADHD groups. Twenty-three patients were drug-naïve, while 13 patients were receiving drug therapy: methylphenidate ($n=6$, 18–36 mg/day), atomoxetine ($n=3$, 30–50 mg/day), aripiprazole ($n=2$, 3 mg/day) and a combination of atomoxetine and methylphenidate ($n=2$, 18–36 and 40–55 mg/day, respectively). One subject was also diagnosed as having a learning disorder; one subject was diagnosed with tic disorder; one subject was diagnosed with oppositional defiant disorder and one with learning and oppositional defiant disorders, according to the DSM-IV criteria.

3.2. Serum OXT levels

As seen in Table 1 and Fig. 1, serum levels of OXT in total subjects with ADHD (the mean ± S.D.: 60.687 ± 37.143 pg/ml) were significantly ($t=4.237$, $d.f.=56$, $P<0.001$) lower than neurotypical controls (the mean ± S.D.: 99.876 ± 28.566 pg/ml). Kruskall–Wallis test detected significant ($P<0.001$) differences in OXT serum levels among the neurotypical control group, the drug naïve ADHD and the drug medicated ADHD groups. Interestingly, serum levels of OXT in the drug medicated ADHD group showed significantly ($P=0.048$) higher than their drug naïve counterparts, while there was no difference ($P=0.072$) between the drug medicated ADHD groups and neurotypical controls. Furthermore, there was a significant negative correlation between OXT serum levels and ADHD-RS total scores (Spearman's correlation: $r=-0.343$, $P=0.040$), and ADHD-RS inattentive scores (Spearman's correlation: $r=-0.352$, $P=0.035$), in all ADHD patients. Meanwhile, there was no correlation between serum levels of OXT

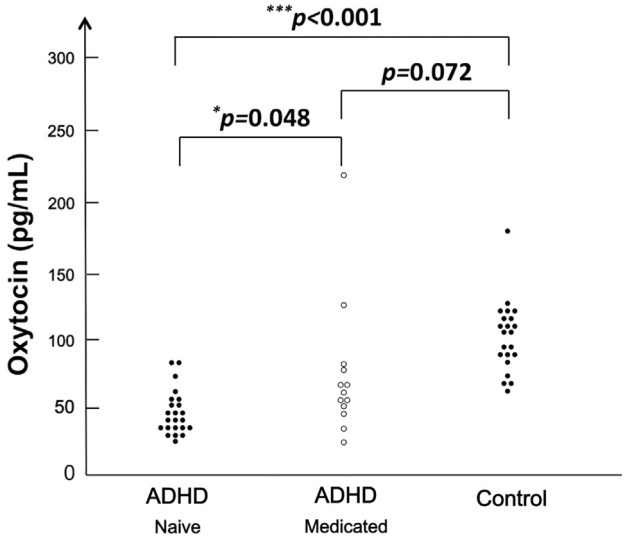

Fig. 1. The serum levels of OXT in neurotypical controls and ADHD patients. The serum levels of OXT in ADHD ($n=36$) were significantly ($P<0.001$, $t=-4.273$, $d.f.=56$) lower than those of neurotypical controls ($n=22$). Kruskall–Wallis test, detected significant differences in OXT serum levels between the neurotypical controls and the drug naïve ADHD and the drug medicated ADHD groups. ($P<0.001$). Mann–Whitney *U* test and Bonferroni post hoc correction detected significant differences between the serum levels of OXT in the drug medicated ADHD group and drug naïve ADHD group ($P=0.048$), while no significant differences between the drug medicated ADHD groups and neurotypical controls ($P=0.072$). Abbreviations: ADHD, Attention Deficit/Hyperactivity Disorder; OXT, Oxytocin.

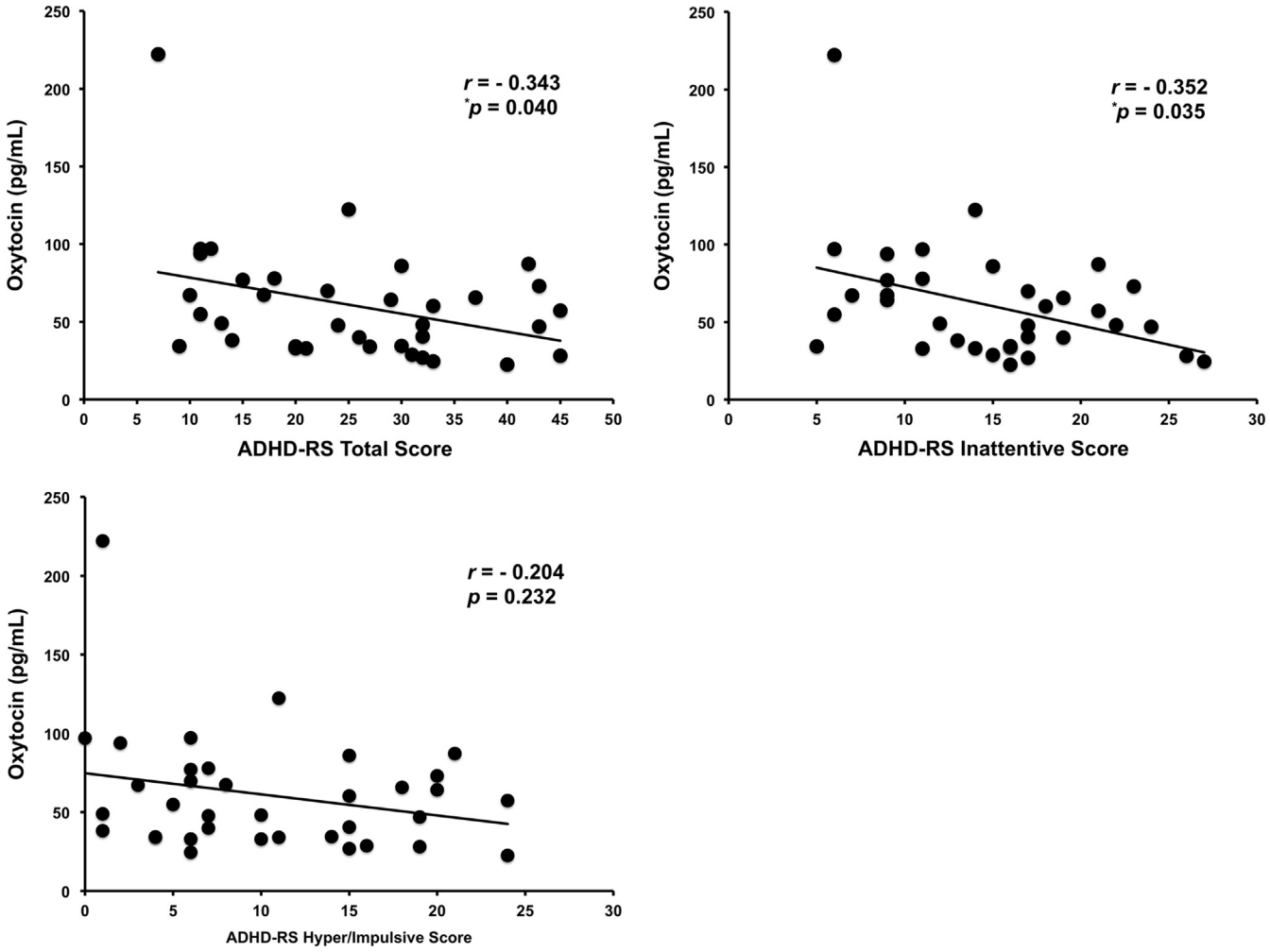

Fig. 2. Relationship between serum levels of OXT and ADHD-RS total scores, inattentive scores and hyperactivity-impulsive scores in ADHD. There were significant negative correlations between ADHD-RS total scores (Spearman's correlation: $r=-0.343$, $P=0.040$) and ADHD-RS inattentive scores (Spearman's correlation: $r=-0.352$, $P=0.035$) with OXT serum levels in patients ($n=36$) with ADHD. However, there was no correlation between serum levels of OXT and ADHD-RS hyperactivity/impulsive scores (Spearman's correlation: $r=-0.204$, $P=0.232$) in these patients. Abbreviations: ADHD, Attention Deficit/Hyperactivity Disorder; ADHD-RS, Attention Deficit/Hyperactivity Disorder-Rating Scale IV Japanese version; OXT, oxytocin.

and ADHD-RS hyperactivity/impulsive scores (Spearman's correlation: $r=-0.204$, $P=0.232$) in the ADHD groups (Fig. 2). Regression analysis revealed no association between the serum levels of OXT in all ADHD patients and their IQ score ($d.f.=1$, $F=2.184$, $P=0.149$).

4. Discussion

In this study, we found that serum OXT levels in total subjects with ADHD were significantly lower than those of age- and sex- matched neurotypical controls. To the best of our knowledge, this is the first report demonstrating decreased serum levels of OXT in ADHD patients. Interestingly, serum levels of OXT were significantly higher in medicated ADHD patients than in drug naïve counterparts. Additionally, there were significant negative correlations between serum OXT levels and ADHD-RS total and inattentive scores in all ADHD patients.

Accumulating evidence highlights the significant role OXT plays in the human limbic system, including the amygdala (Bale et al., 2001; Landgraf and Neumann, 2004; Huber et al., 2005; Domes et al., 2007). Experimental animal studies suggest that the social memory effects of OXT are mediated by the amygdala (Ferguson et al., 2001, 2002), hinting at an important role for the amygdala in mediating the socio-affective action of OXT. A recent meta-analysis showed that alterations in limbic regions, such as the anterior cingulate cortex and amygdala, are more pronounced in untreated ADHD populations, and that these changes seemed to diminish over time from childhood to adulthood in ADHD patients (Frodl and Skokauskas, 2012). This study also found that treatment for ADHD patients appeared to confer a beneficial effect on brain structure (Frodl and Skokauskas, 2012). It is highly likely that the pathophysiological effect of ADHD therapies involve OXT regulation and the amygdala.

Lower levels of peripheral OXT have been reported in some studies on ASD, depression and schizophrenia, although the findings vary (Modahl et al., 1998; Green et al., 2001; Macdonald and Feifel, 2012; Meyer-Lindenberg et al., 2011; Striepens et al., 2011; Yamasue et al., 2012; Stavropoulos and Carver, 2013). In contrast, a positive correlation was found between OXT levels and symptom severity in patients with social anxiety disorder (Striepens et al., 2011), indicating that excessive attention may raise peripheral OXT levels. Interestingly, our study found a negative correlation between OXT levels and inattentiveness in ADHD patients. Therefore, peripheral OXT levels might be associated with attention deficit symptoms. It has also been suggested that peripheral OXT levels may indicate a sensitivity to socially-relevant information (Bartz et al., 2011). Previous study shows that plasma OXT was negatively associated with daily living skills and interpersonal relations (Vineland Adaptive Behavior Scale scores)

in the ASD group (Modahl et al., 1998). Furthermore, plasma OXT-extended form was correlated positively with an Autistic Disorders Checklist (ADC) item, regarding the presence of stereotypies and negatively with an ADC item regarding abnormalities in comfort-giving within the ASD group (Green et al., 2001). However, plasma OXT levels of their reports including ASD and controls are very low or the under the limitation (0–6 pg/ml), although serum levels of OXT in our study are detectable (22–222 pg/ml). The reasons for this discrepancy are currently unknown. One possibility of this discrepancy may be the difference in the source of blood sample (serum vs plasma). Another possibility is due to ethnic difference (Caucasian vs Japanese). Nonetheless, further studies using larger sample sizes will be needed to address these points.

Recently, it is shown that genetic variations of the OXT receptor gene influenced social cognition, and that this association may be present in other diagnostic groups that display impaired social communication (Park et al., 2010). Furthermore, recent evidence shows that OXT improves emotion recognition and social approach in people with ASD (Guastella et al., 2009; Andari et al., 2010; Kosaka et al., 2012), suggesting that it may have therapeutic implications for individuals with ADHD and other diagnoses with social cognitive deficits.

Recently, it has been reported that intranasal administration of OXT (24IU) enabled ASD patients to make nonverbal information-based judgments more frequently, with a shorter response time (Watanabe et al., 2014). In addition, during the test period, OXT increased diminished brain activity in the medial prefrontal cortex, typically seen in ASD patients (Watanabe et al., 2014). Moreover, OXT enhanced functional coordination in the area, and the magnitude of these neural effects was predictive of the behavioral effects in ASD sufferers (Watanabe et al., 2014). Therefore, it is likely that OXT treatment may confer beneficial effects on the sociocommunicational deficits of ADHD, in a similar manner to ASD, especially since previous studies showed that reduced cortical thickness in the medial prefrontal cortex is associated with a worse prognosis for ADHD (Shaw et al., 2006). Although the development of OXT for therapeutic use is still in the early stages, its ability to increase trust and enhance emotional empathy suggests considerable potential in neuropsychiatry. This could be either as an addition to other medications, or in combination with psychotherapy for ADHD and other diagnoses with social cognitive deficits.

The main limitation of this study is its small sample size. Furthermore, we did not compare the serum levels of OXT in ASD patients, although ADHD and ASD are highly comorbid. Therefore, further studies using larger sample sizes of ASD cohorts will be needed to confirm these results.

In conclusion, this study suggests that decreased levels of OXT may play a role in the pathophysiology of patients with ADHD and its inherent inattentiveness, although further research is needed in this area.

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Competing interests

The authors declare that they have no competing interests.

Author contributions

TsuSas conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted.

YO, TI, TK, JT, YK, HirKim TN, HidKom, MasIsh, TadHas, AS, TasHas, NK and TetShi carried out the initial analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted.

KH and MasIyo designed the data collection instruments, and coordinated and supervised data collection, critically reviewed the manuscript, and approved the final manuscript as submitted.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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